Polyglutamine-expanded androgen receptor interferes with TFEB to elicit autophagy defects in SBMA.

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Public Summary:
In this work, we use induced pluripotent stem cells from individuals with spinal and bulbar muscular atrophy (SBMA) to generate neural precursor cells and study the disease in a dish. We found that SBMA cells have metabolic defects leading to cell death that could explain some of the disease clinical manifestations.

Scientific Abstract:
Macroautophagy (hereafter autophagy) is a key pathway in neurodegeneration. Despite protective actions, autophagy may contribute to neuron demise when dysregulated. Here we consider X-linked spinal and bulbar muscular atrophy (SBMA), a repeat disorder caused by polyglutamine-expanded androgen receptor (polyQ-AR). We found that polyQ-AR reduced long-term protein turnover and impaired autophagic flux in motor neuron-like cells. Ultrastructural analysis of SBMA mice revealed a block in autophagy pathway progression. We examined the transcriptional regulation of autophagy and observed a functionally significant physical interaction between transcription factor EB (TFEB) and AR. Normal AR promoted, but polyQ-AR interfered with, TFEB transactivation. To evaluate physiological relevance, we reprogrammed patient fibroblasts to induced pluripotent stem cells and then to neuronal precursor cells (NPCs). We compared multiple SBMA NPC lines and documented the metabolic and autophagic flux defects that could be rescued by TFEB. Our results indicate that polyQ-AR diminishes TFEB function to impair autophagy and promote SBMA pathogenesis.